

REVIEW

REVIEW OF SUCCINATE DEHYDROGENASE-DEFICIENT RENAL CELL CARCINOMA WITH FOCUS ON CLINICAL AND PATHOBIOLOGICAL ASPECTS

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Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) was first identified in 2004 and has been integrated into the 2016 WHO classification of RCC. Succinate dehydrogenase (SDH) is an enzyme complex composed of four protein subunits (SDHA, SDHB, SDHC and SDHD). The tumor which presents this enzyme mutation accounts for 0.05 to 0.2% of all renal carcinomas. Multiple tumors may occur in approximately 30% of affected patients. SDHB-deficient RCC is the most frequent, and the tumor histologically consists of cuboidal cells with eosinophilic cytoplasm, vacuolization, flocculent intracytoplasmic inclusion and indistinct cell borders. Ultrastructurally, the tumor contains abundant mitochondria. Immunohistochemically, tumor cells are positive for SDHA, but negative for SDHB in SDHB-, SDHC- and SDHD-deficient RCCs. However, SDHA-deficient RCC shows negativity for both SDHA and SDHB. In molecular genetic analyses, a germline mutation in the *SDHB*, *SDHC* or *SDHD* gene (in keeping with most patients having germline mutations in an *SDH* gene) has been identified in patients with or without a family history of renal tumors, paraganglioma/pheochromocytoma or gastrointestinal stromal tumor. While most tumors are low grade, some tumors may behave in an aggressive fashion, particularly if they are high nuclear grade, and have coagulative necrosis or sarcomatoid differentiation.

Key words: succinate dehydrogenase, renal cell carcinoma, review.

Introduction

Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) was identified by Vanharata *et al.* in 2004 and been accepted by the 2016 WHO organization of renal tumors as a unique subtype of RCC. In

2013, it was integrated into the ISUP (International Society of Urological Pathology) Vancouver Classification published as a provisional entity [1, 2, 3]. Since its first description, some recent large studies dealing with this tumor have been reported [4, 5, 6, 7]. The

tumor entity morphologically and genetically seems to show a wider spectrum than has been hitherto recognized [6, 7, 8, 9, 10, 11]. In this article, we review the clinicopathological aspects of this tumor.

Epidemiology and clinical features

The frequency of SDH-deficient RCC is estimated as between 0.05 to 0.2% of all renal carcinomas [7]. Among SDH-deficient RCCs, SDHB-mutated RCC is the most frequent [1, 2, 3, 4, 5, 6, 7, 8, 10], followed by SDHC and SDHD-deficient RCC [5, 7, 9]. Very recently, one case with SDHA-deficient RCC has been described [11]. The lifetime risk of renal tumor in patients with the *SDHB* gene mutation has been estimated as 14% [12]. The age of patients ranges from 22 to 72 years, with a mean age of 40 years in Williamson's series and from 14 to 76 years with a mean age of 37 years in Gill's series [6, 7]. There is a slight male predominance [6, 7]. The association with paraganglioma/pheochromocytoma or type 2 gastrointestinal stromal tumor has been reported [1, 2, 3, 4, 5, 6]. SDH-deficient gastrointestinal stromal tumors and paragangliomas are also known to be associated with the syndromic, non-hereditary Carney triad of paraganglioma, pulmonary chondroma and SDH-deficient gastrointestinal stromal tumor. Due to the lifelong 14% risk of developing a renal neoplasm, genetic testing in the appropriate clinical context should be considered for patients with this constellation of tumors.

Pathological findings

Macroscopic findings

The size of the tumor ranges from 20 mm to 200 mm in Williamson's series and from 7 to 90 mm with a mean of 51 mm in Gill's series [6, 7]. Gross-

ly, the tumors are usually well circumscribed and the cut surface shows tan to red, tan to brown, or red to brown color [6, 7]. Hemorrhage or partial cystic change may sometimes be observed [6, 7]. Bilateral tumors have been reported in approximately 30% of patients [6, 7].

Microscopic findings

SDHB-deficient renal cell carcinoma

In this subtype, various patterns overlapping with other known histological subtypes including chromophobe RCC, clear cell RCC, papillary RCC, sarcomatoid RCC, unclassified RCC and renal oncocytoma have been described [1, 2, 3, 4, 5, 6, 7, 8, 10]. In the early reports, the morphology of the tumors was generally never illustrated [4]. Among them, oncocytic carcinoma with a unique morphology was most frequently observed [3, 4, 5, 6, 7]. We now recognize this as a unique tumor type with the following characteristic features: 1) the tumor is composed of nested, tubular and solid architecture with variable cysts; 2) the tumor cells are cuboidal with eosinophilic cytoplasm containing typical cytoplasmic vacuoles or flocculent inclusions which when prominent impart a bubbly appearance; 3) the nuclei are homogeneous, have smooth nuclear contours, evenly distributed chromatin and a neuroendocrine appearance with inconspicuous nucleoli [3, 4, 5, 6, 7] (Fig. 1A, B); 4) entrapped tubules or glomeruli are observed at the peripheral edges of the tumor [6, 7]. Mast cells often infiltrate the intratumoral stroma [6, 7].

SDHC- and SDHD-deficient renal cell carcinomas

These tumors generally show morphology comparable with clear cell RCC [5, 9]. In one SDHC-deficient case, papillary RCC has also been described [9].

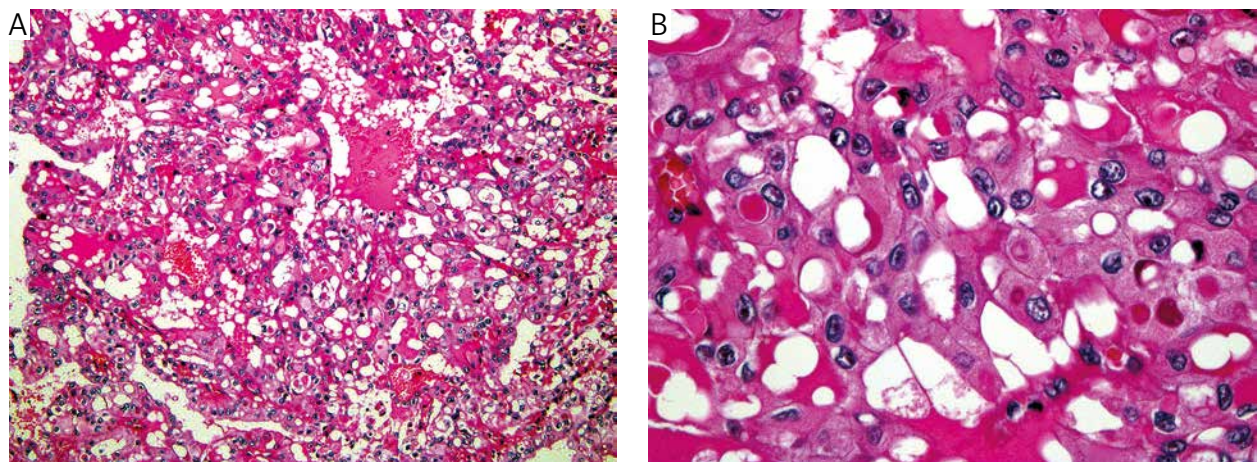


Fig. 1. Microscopic findings. A) The tumor consists of eosinophilic to oncocytic cells with multiple cytoplasmic vacuoles and an indistinct cell border. B) At higher magnification, some cytoplasmic inclusions are observed

SDHA-deficient renal cell carcinoma

One case of SDHA-deficient RCC showed unclassified RCC characteristics of both papillary RCC and collecting duct carcinoma [11].

Immunohistochemical findings

SDH-deficient RCCs are generally immunoreactive for PAX8 and Ksp-cadherin, but negative for c-kit, RCC Ma, p63 and CA9 [3, 4, 6, 7]. The immunoreactivity for epithelial markers is negative or focal. Immunohistochemical loss of SDHB is a diagnostic requirement. In SDHB-, SDHC- and SDHD-deficient RCCs, tumor cells are negative for SDHB (Fig. 2), but positive for SDHA [3, 4, 6, 7, 13]. In contrast, tumor cells in SDHA-deficient RCC show negativity for both SDHA and SDHB [11]. Neuroendocrine markers are negative.

Ultrastructural findings

In SDHB-deficient RCC, the cytoplasm of tumorous cells contains abundant mitochondria and cytoplasmic inclusions correspond to abnormal mitochondria with degenerating cristae and ground substance [13].

Molecular genetic findings

SDH-deficient RCC is strongly hereditary with the vast majority demonstrating germline mutations in one of the SDH related genes. A germline mutation in SDHB, SDHC or SDHD has been identified [1, 2, 3, 4, 5, 6, 7, 9, 12, 13]; SDHB mutations are most common followed by SDHC. SDHB-deficient RCCs seem to harbor mutations that alter arginine codons, and loss of the second allele is frequent [1, 6]. In SDHC-deficient RCC, tumor cells showed loss of heterozygosity (LOH) for intragenic and flanking markers of the *SDHC* gene locus [9].

Differential diagnosis

The following renal tumors should be taken into consideration in the differential diagnostic process: chromophobe RCC, clear cell RCC, hybrid oncocyctic/chromophobe tumor (HOCT), renal oncocytoma, renal oncocytosis, acquired cystic disease (ACD)-associated RCC, Birt-Hogg-Dubé (BHD) syndrome-associated RCC, hereditary leiomyomatosis RCC syndrome (HLRCC), and PTEN hamartoma syndrome. In chromophobe RCC, the tumor generally consists of pale and eosinophilic cells with distinct cell borders, perinuclear haloes, nuclear irregularities and occasional binucleated cells [14]. Tumor cells generally demonstrate diffuse positivity for cytokeratin 7, CD117 and Ksp-cadherin [15, 16]. Clear cell

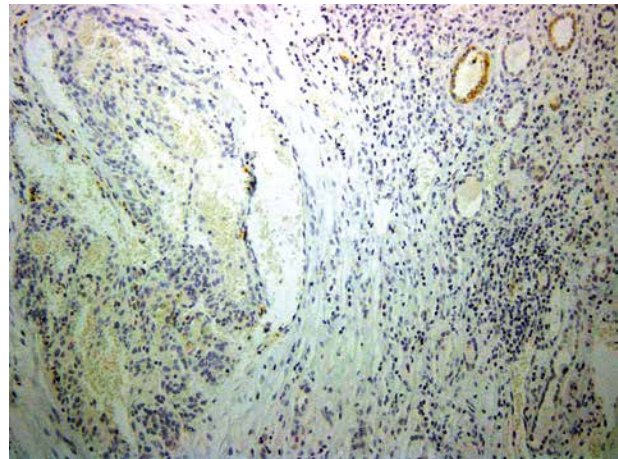


Fig. 2. Immunohistochemical findings of SDHB protein. The tumor cells are completely negative for SDHB. At contrast, normal tubules are positive

RCC generally consists of clear cells with a varying growth pattern including alveolar, solid, acinar and cystic pattern and shows diffuse membranous positivity for CA9 and vimentin [15]. The cytoplasm may sometimes be prominently eosinophilic and with the nested architecture is an important mimic of SDH-deficient RCC. The SDHB immunohistochemistry may be problematic to interpret and may be weak in clear cell carcinoma due to the abundant clear cytoplasm; this should not be interpreted as benign negative. HOCT shows hybrid morphology of both chromophobe RCC and renal oncocytoma, namely uniform-sized tumor cells with eosinophilic cytoplasm, round nuclei and perinuclear haloes. In renal oncocytoma, a nesting growth pattern is often observed in the background of edematous or hyalinized stroma [17, 18]. Some patients with renal oncocytosis may have a history of chronic renal failure or dialysis [19]. In BHD syndrome-related RCCs, HOCT is the most frequent. The clinical association with cutaneous (fibrofolliculoma, trichodyscomas or acrochordon) and pulmonary (cyst and pneumothorax) lesions is very important. The germline mutation of the *FLCN* gene is very important for the definite diagnosis of BHD syndrome [20]. In HLRCC, tumor cells usually correspond to papillary RCC, type 2 and have eosinophilic prominent nucleoli resembling cytomegalovirus inclusion. Recently, the spectrum of architectural patterns has been expanded: papillary, tubulopapillary, tubular, cribriform, solid and cystic. Most patients have also cutaneous and/or uterine leiomyomas clinically [21]. However, it was reported in recent papers that synchronous or metachronous occurrence of RCC and leiomyoma is relatively rare. In PTEN hamartoma syndrome, patients have trichilemmoma, thyroid cancer, uterine corpus cancer or breast cancer clinically [22]. Additionally, tumor cells show immunohistochemical negativity for PTEN.

Therapy and clinical management

An immediate surgical intervention should be recommended [23]. Nephron-sparing surgery should be generally selected when a solid tumor is present and is at the early stage. Active surveillance only is not recommended [24]. In advanced disease, FDG-PET examination is recommended [5]. In cases with metastatic disease, molecular targeted therapy for vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), and tyrosine kinase (TK) has been previously administered [11, 25]. We are not aware of a report where the patient was treated with ablative therapy. Some authors have proposed that if the patients exceed the age 40 to 45 and have no family history of renal tumor, the molecular analyses of SDHB may be unnecessary [8]. However, in patients under age 45 the possible diagnosis of SDH-deficient RCC should be considered even in the absence of family history [5]. Clinico-pathologic correlation is key and management in a multidisciplinary setting is optimal.

Prognosis

It is well known that a subset of SDH-deficient RCC has potential to behave aggressively [4, 5, 7, 11, 23, 26]. However, tumors with low grade nuclear morphology behave in an indolent fashion after the complete resection [4]. Tumor with high grade nuclear features, coagulative necrosis or sarcomatoid differentiation may behave in an aggressive fashion, and the observation of any of these features needs to be documented in the pathology report [7]. Metastases to the liver, bone, brain, lung and lymph nodes have been documented [4, 5, 6, 7, 11, 25].

Future perspectives

In the screening for the detection of SDH-deficient RCC, the immunohistochemistry of both SDHA and SDHB proteins is available [4, 5, 7, 27]. However, pathologists need to pay attention to the immunohistochemical interpretation of these proteins, because clear cell RCC tends to show more false negatives for SDHB protein than other histological types [28]. In SDHA-deficient RCC, whether or not germline mutation of the SDHA gene exists remains unknown [11]. Accordingly, a more consistent number of cases and the germline mutation analysis of the SDHA gene are necessary. In order to clarify the relationship between SDHC- or SDHD-deficient RCCs and histological type or clinical behavior, further examination in a large scale study will be needed.

The authors declare no conflict of interest.

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